UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,388	03/26/2004	Gerry Shaw	5853-400	8619

30448 7590 03/05/2009
AKERMAN SENTERFITT
P.O. BOX 3188
WEST PALM BEACH, FL 33402-3188

EXAMINER	
GUCKER, STEPHEN	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
03/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,388	SHAW ET AL.	
	Examiner	Art Unit	
	STEPHEN GUCKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) *7,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments

1. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn. Applicant's amendment to the claims filed 12/1/08 have obviated all of the grounds of rejections made in the previous Office Action filed 5/30/08 under U.S.C. 112, 1st paragraph. However, the wording of the current amendment has resulted in a new rejection under U.S.C. 112, 2nd paragraph as indicated below.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 3, 6, and 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has indicated that page 3, lines 29-31 of the specification is where support is found for amending the claims to read "wherein NF-H can be detected in quantities as low as 50 pg". However, it is unclear and vague in what volume such detection could be achieved. It is one thing to say that 50pg could be detected in 50µl, but quite another to say that 50pg could be detected in 50ml or 50L because of the high dilution/low concentration of said 50pg in a large volume making it correspondingly harder to detect as the 50pg analyte becomes further diluted. Therefore, the metes and bounds of the claims are indefinite due to the lack of recitation of volume to be analzyed in the instant methods for detecting quantities as low as 50pg. The grounds of this rejection could be obviated by reciting more fully the specification on page 3, lines 29-31 where it is disclosed that the "current version of this assay can reliably detect NF-H in small 50µl volumes in

quantities as low as 50pg". For example, the claims could be amended to read "wherein NF-H can be detected in quantities as low as 50pg in 50µl".

4. Claims 1, 3, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. ("Hu") in view of Zemlan for reasons of record and the following. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Hu (March 8, 2002) teaches a method of detecting neuronal injury in subjects with Alzheimer's disease (AD) and vascular dementia by using ELISA with antibodies that bind NF-H found in CSF samples taken from the subjects (abstract, Figures 2-3). Hu does not teach using blood samples. Zemlan teaches a method of detecting neuronal injury in subjects by using ELISA with antibodies that bind neurofilament proteins found in blood samples taken from the subjects (abstract and column 3, line 25 to column 4, line 42). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the methods of Hu with the blood samples of Zemlan because it is simpler and easier to procure a blood sample and assay it by ELISA than it is to procure a CSF sample by lumbar puncture because the blood sample can be simply taken from the arm (no usual side effects) while the CSF sample needs to be taken from the spinal cord region with the attendant risks of damaging the cord and then producing the side effects usually resulting from lumbar puncture such as headaches. The

instant invention is *prima facie* obvious because the artisan would be motivated to take a simple venous blood sample (less time consuming than even a routine blood donation) than take a riskier CSF sample from the spinal cord region.

Applicant's arguments filed 12/12/07 have been fully considered but they are not persuasive because Applicant argues that Zemlan is not enabling and that at the time of the invention one would not have known that NF-H could be detected in blood, serum or plasma from an injured mammal and used as a marker for neuronal injury, and that this was an unexpected result. However, Zemlan discloses this unexpected result of finding large proteins migrating from the CSF into the bloodstream of injured or diseased patients:

> It would not be expected that cleaved-tau levels would also be elevated in serum in these patients as blood is compartmentalized from CSF by the blood-brain-barrier. The fundamental basis for compartmentalization between blood and CSF is the tight junctions that exist between endothelial cells that comprise the blood-brain-barrier (Saunders NR, Habgood MD and Dziegielewska. (1999) Barrier mechanisms in the brain, I. Adult brain. Clin. Exp. Pharmacol. Physiol. 26: 11-19). These tight junctions exclude all but the smallest proteins (less than 5 kDa molecular weight). As cleaved-tau is much larger, demonstrating an average molecular weight of 40 kDa, one skilled-in-the-art would not expect to find cleaved-tau in serum of these patients. Surprisingly, when we examined patients undergoing neuronal degeneration resulting from sever head injury or stroke, we found elevated levels of serum cleaved-tau in both groups of patients (Table 2). The cause of this unexpected elevation in both CSF and serum cleaved-tau is unknown, however, the elevation in serum cleaved-tau may be related to disruption of the blood-brain-barrier that is disease-associated. (column 14, lines 41-61).

Therefore, given Zemlan's disclosure and working example that tau protein from the CSF could "leak" into and be detected in the bloodstream of patients at levels ranging from 0.14 - 4.56ng/ml (equivalent to 0.14 – 4.56pg/µl, see Table 2), it would have been obvious to look for NF-H as well, because Zemlan suggests it. See especially column 3, lines 51-56;

column 5, line 50 to column 6, line 11; column 21, lines 9-22; and Table 2. The expectation of success is provided by Hu because of the working examples of detecting neuronal injury in subjects with Alzheimer's disease (AD) and vascular dementia by using ELISA with antibodies that bind NF-H in CSF samples. Given Zemlan's disclosure and direct suggestion to detect NF-H in blood, it would have at least been obvious to try to use the methods of Hu on blood samples. Therefore, in addition to the invention being obvious to succeed for the reasons already of record, the combined references also make the invention obvious to try because all the claimed elements (NF-H, the process steps of detection, the patient population, and the disorders) were known in the prior art from a finite number of choices and one skilled in the art could have combined the elements as claimed by known methods of detection such as ELISA with no change in their respective functions (the NF-H was known to increase in CSF from neurological disorders, it was known it could be detected by ELISA, and other large neuronal proteins from degenerating axons were now known to be found in blood, so it was no longer an unexpected result), and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See KSR Int'l Co. v. Telefex Inc., 127 S. Ct. 1727 (U.S. 2007).

Applicant's arguments filed 12/1/08 have been fully considered but they are not persuasive because Applicant argues that Zemlan is not an enabling reference because Zemlan discloses an ELISA for tau when assaying CSF samples which is asserted to be several orders of magnitude less sensitive than the instant method. This is simply incorrect. As noted previously, Zemlan's sensitivity ranges from 0.14 - 4.56ng/ml (equivalent to 0.14 – 4.56pg/µl, see Table 2) when assaying from serum samples, not CSF samples, and CSF

sampling is not a limitation of the instant claims. Also see column 21, lines 9-22. Also, Applicant argues that Zemlan is not enabling because he measures tau and not NF-H, and that measuring NF-H at a sensitivity as low as 50pg as recited in claim 1 distinguishes over the art. This is not persuasive because ELISA methods using antibodies routinely measure proteins below the 1pg/µl or 50pg/50µl level of sensitivity. For example, see IDS filed 1/30/06, the Hornbeck et al. reference, page 11.2.16, where bacterial proteins are measured below 1ng/ml, which equals less than 1pg/µl, which is less than 50pg/50µl. Hornbeck et al. on page 11.2.21 states that "antibody-sandwich assays are generally the most sensitive ELISA configurations and can detect concentrations of protein antigens between 100pg/ml and 1ng/ml….Either the direct or sandwich ELISA may be used to detect and quantitate a bacterially expressed antigen or a purified or partially purified antigen in the range of 1ng/ml to 1µg/ml." First, Hornbeck et al. directly state that ELISA methods can measure proteins at a level of sensitivity 10 times more sensitive than the instant method (100pg/ml equates to 0.1ng/µl or 5pg/50µl). Note than Hornbeck et al. do not and need not specify which bacterial protein antigen they are referring to because this is a general statement referring to any protein, absent evidence to the contrary. Applicant has provided no evidence as to why the protein antigen in question, NF-H, cannot be detected in the normal and routine range by antibodies using ELISA methods. Applicant also argues Hu in isolation, saying that Hu does not suggest the claimed invention. As previously noted, Zemlan explicitly suggests the claimed invention, see especially column 3, lines 51-56 and column 5, line 50 to column 6, line 11.

In response to Applicant's argument that CSF is vastly easier to work with than blood, the fact that Applicant has recognized another advantage which would flow naturally from

following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See Ex parte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). As stated previously, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the methods of Hu with the blood samples of Zemlan because it is simpler and easier to procure a blood sample and assay it by ELISA than it is to procure a CSF sample by lumbar puncture because the blood sample can be simply taken from the arm (no usual side effects) while the CSF sample needs to be taken from the spinal cord region with the attendant risks of damaging the cord and then producing the side effects usually resulting from lumbar puncture such as headaches. The instant invention is prima facie obvious because the artisan would be motivated to take a simple venous blood sample (less time consuming than even a routine blood donation) than take a riskier CSF sample from the spinal cord region.

In addition to the invention being obvious to succeed for the reasons already of record, the combined references also make the invention obvious to try because all the claimed elements (NF-H, the process steps of detection, the patient population, and the disorders) were known in the prior art from a finite number of choices and one skilled in the art could have combined the elements as claimed by known methods of detection such as ELISA with no change in their respective functions, (the NF-H was known to increase in CSF from neurological disorders, it was known it could be detected by ELISA, and other large neuronal proteins from degenerating axons were now known to be found in blood, so it was no longer an unexpected result) and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See KSR Int'l Co. v. Telefex Inc., 127 S. Ct.

1727 (U.S. 2007). Therefore, contrary to Applicant's assertions that extensive experimentation would need to be involved, the results were not unexpected but explicitly suggested by the prior art (no extensive conception of invention necessary), the level of sensitivity of the claimed assay was not extraordinarily sensitive (no extensive experimentation needed to produce extraordinary sensitivity), and even if there were no reasonable expectation of success (although the Examiner believes he has provided evidence on the record that there was a reasonable expectation of success), it was at the very least obvious to try in a manner consistent with the precedent set by KSR Int'l Co. v. Telefex Inc., 127 S. Ct. 1727 (U.S. 2007).

5. Claims 1, 3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. ("Hu") in view of Zemlan as applied above, and further in view of Grainger et al. (US 5,595,722; "Grainger"). Grainger discloses that chicken polyclonal antibodies are suitable to be used in ELISAs to routinely detect and assay proteins such as TGF-β in serum and plasma samples (Example 8). Therefore, the use of chicken polyclonal antibodies in combination with the previously applied art would have yielded predictable results to one of ordinary skill in the art at the time of the invention, absent evidence to the contrary. See KSR Int'l Co. v. Telefex Inc., 127 S. Ct. 1727 (U.S. 2007).

Applicant's arguments filed 12/1/08 have been fully considered but they are not persuasive because Applicant reiterates his previous arguments concerning the Hu and Zemlan references as being not enabled, the claimed invention producing unexpected results, and the prior art not demonstrating the required sensitivity to detect 50pg of NF-H. These arguments have been rebutted as set forth in ¶4 set forth above.

6. Claims 1, 3, 6, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. ("Hu") in view of Zemlan as applied above, and further in view of Posmantur et al. (IDS filed 1/30/06; "Posmantur"). Posmantur discloses that NF-H levels in the brain begin to decrease as soon as 3 hours post-injury (pages 539-540). Therefore, it would be obvious to try to look for the missing NF-H protein from the brain in the blood within a few hours of a neuronal injury as taught by Posmantur with the methods disclosed by Hu and Zemlan, and the combination with the previously applied art would have yielded predictable results to one of ordinary skill in the art at the time of the invention, absent evidence to the contrary. See KSR Int'l Co. v. Telefex Inc., 127 S. Ct. 1727 (U.S. 2007).

Applicant's arguments filed 12/1/08 have been fully considered but they are not persuasive because Applicant reiterates his previous arguments concerning the Hu and Zemlan references as being not enabled, the claimed invention producing unexpected results, and the prior art not demonstrating the required sensitivity to detect 50pg of NF-H. These arguments have been rebutted as set forth in ***¶4*** *set forth above. Additionally, Applicant argues it would not have been obvious to try to detect the missing NF-H protein from brain as taught by Posmantur in blood. This is unconvincing due to the extremely finite outcomes possible as to the possible disposition of the missing NF-H protein. One, it could be completely degradated inside the neuron as Applicant argues and not be found in blood. Two, it could be released into the CSF and not escape into the blood as taught by Zemlan and again, not be found in blood. Three, it could be released into the CSF and escape into the blood as taught by Zemlan and this time, be found in blood. Given only three logical possibilities, the Examiner's position is that it would be obvious to try to locate the missing NF-H in blood as the missing NF-H could*

only arrive at three very predictable fates, and measuring the NF-H level in an easily drawn blood sample would have obvious advantages over either a surgical brain biopsy or spinal tap, so it would be obvious to try to assay NF-H, and a positive or negative result would be relatively easy to obtain for the ordinary artisan.

7. The declaration under 37 CFR 1.132 filed 12/1/08 is insufficient to overcome the rejection of claims 1,3, 6, and 11-12 based upon U.S.C. 103 as set forth in the last Office action because: the declarant argues that "the trick is knowing which of the numerous possible candidates to focus on," referring to NF-H as opposed to any other brain protein. This is not persuasive because Zemlan explicitly directs the ordinary artisan to focus on NF-H from a finite list of 3 neurofilament proteins and/or tau. Declarant asserts that many brain-specific proteins are not resistant to proteases, and do not present themselves in blood following injury or disease. Again, this is unpersuasive because Zemlan suggests assaying for NF-H which apparently meets the declarant's criteria. Declarant repeatedly argues in generalities about many proteins, but not to the individual claims of the Application, drawn to NF-H, as suggested by Zemlan. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

Declarant argues against Hu by asserting that Hu's assay was never calibrated with pure NF-H so the actual amounts of NF-H being detected are not known. This assertion is unconvincing because Hu does use a specified amount of 250pg/ml of tau protein to check if cross-reaction is occurring between the antibody he is using to detect NF-H and tau. Hu states that there was no increase over the reagent control, which would be NF-H (page 158). Therefore, Hu was expecting that if cross-reactivity were occurring, a level of tau protein

equivalent to 0.250pg/µl or 12.5pg/50µl would be sufficient to produce cross-reactivity or erroneously high measurements of NF-H in his assay, if the antibody he was using could also bind to tau, which from the result obtained, it was not. The amount of tau protein Hu was employing to double-check the specificity of his antibody specific for NF-H was less than the amount of protein used in the claimed method. In addition, as previously stated by the Examiner, Hornbeck et al. directly state that ELISA methods can measure proteins at a level of sensitivity 10 times more sensitive than the instant method. The assertion made by declarant concerning the sensitivity of Hu's antibody is unsupported either by any objective evidence provided by declarant or what is known to be routine in the prior art. Declarant's need for supporting his assertions is especially pertinent when declarant (Dr. Gerry Shaw) is one of the inventors of the claimed invention and is not a disinterested party.

Declarant makes statements directed to potential serious problems that could have arisen and the surprise that the claimed invention worked as intended. These statements amount to an affirmation that the claimed subject matter functions as it was intended to function. This is not relevant to the issue of nonobviousness of the claimed subject matter and provides no objective evidence thereof. See MPEP § 716.

Declarant makes statements directed to the commercial success of the claimed invention. However, declarant's statements are drawn to specific dollar amounts and percentage of royalty sales, and not to market share. Gross sales figures do not show commercial success absent evidence as to market share, *Cable Electric Products, Inc. v. Genmark, Inc.*, 770 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985), or as to the time period during which the product was sold, or as to what sales would normally be expected in the market, *Ex*

parte Standish, 10 USPQ2d 1454 (Bd. Pat. App. & Inter. 1988). Furthermore, while the sublicensees package reagents into kits for resale, or use the reagents to validate the assay and modify it to use in their standard kit formats, this is not commensurate with the claimed invention of a method (not a kit) to detect neuronal injury by measuring in blood, serum, or plasma with an antibody the presence of NF-H and correlating the presence or amount of NF-H in the sample with the neuronal injury. This is especially true if one licensee's intention is to "validate the assay and modify it to use in their standard kit format." To be pertinent to the issue of nonobviousness, the commercial success of devices falling within the claims of the patent must flow from the functions and advantages disclosed or inherent in the description in the specification. Furthermore, the success of an embodiment within the claims may not be attributable to improvements or modifications made by others. *In re Vamco Machine & Tool, Inc.,* 752 F.2d 1564, 224 USPQ 617 (Fed. Cir. 1985). Also see *EWP Corp. v. Reliance Universal, Inc.,* 755 F.2d 898, 225 USPQ 20 (Fed. Cir. 1985) (evidence of licensing is a secondary consideration which must be carefully appraised as to its evidentiary value because licensing programs may succeed for reasons unrelated to the unobviousness of the product or process, e.g., license is mutually beneficial or less expensive than defending infringement suits).

Finally, declarant makes statements drawn to the utility of the claimed invention, the number of publications arising from it, the number of grants arising from it, the avenues of research it has opened up, the publicity it has garnered, etc. While the Examiner is sincerely impressed by both declarant and his claimed invention and wishes him well and continued

success in these areas, unfortunately, these arguments have little bearing on the invention's nonobviousness.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is 571-272-0883. The examiner can normally be reached on Mondays through Fridays from 0930 to 1800.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/S. G./

Examiner, Art Unit 1649

Stephen Gucker

March 5, 2009

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649